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Microperimetric biofeedback training: fundamentals, strategies and perspectives

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1. ABSTRACT

Microperimetric biofeedback training (MBFT) is a visual rehabilitative strategy based on fixation stability improvement reinforcing or creating a new preferential fixation locus. The rationale consists in reeducating visual system to a new visual condition, promoting retina-brain transmission, and thus cortical plasticity. The use of MBFT found is major application in visual diseases involving central vision, but later it revealed promising functional outcomes even in myopia, inherited retinal degenerations and nystagmus. However, the use of microperimetric biofeedback is still limited due to poor knowledge of the procedure and inconsistent standards of practice, and thus an incipient skepticism on its efficacy. This review provides an overview of the rationale, current implications, procedures and future perspectives of microperimetric biofeedback training.

2. INTRODUCTION

Low-vision rehabilitation (LVR) is a comprehensive term that includes different techniques used to help patients with minimal residual function in improving visual performance and consequently quality of life. In the past, rehabilitation measures included advanced optical aids and educational methods to use these aids and exploit residual vision.(1) Nowadays, the LVR provides an integrated approach taking into account different aspects of visual dysfunction, such as resolution, recognition, contrast sensitivity and binocularity for the visual acuity function, macular and peripheral residual visual fields, residual oculomotor functions and the impact of photostress, glare and color contrast.(2)

Visual fixation is an essential substrate for visual perception, which is known as the time between two consecutive saccadic movements. The eye is not completely static during a fixation task, small involuntary movements such as microsaccades, tremor and drift help to maintain fixation.(3–5) This phenomenon allows to maintain the target of our observation as much as possible upon foveola compensating head movements and neural adaptation.(6)

It is usually assumed that retinal location adopted for fixation corresponds to the foveal center, even if some displacements from this location have been reported.(7) Fixation stability is usually affected in

people with central vision loss, patients appear to use a larger retinal area for fixation when asked to fixate on a target that is away from the primary position gaze. In this regard, fixation instability leads movements toward and further away from the fovea during target fixation, reducing the visibility and accordingly reading rates. The improvement in fixation stability is one of the main goals in microperimetric training programs allowing concurrent gain in the visual function.(8–11).

Eye movements are directly involved in the reading process. A succession of fixations and their subsequent integration constitutes eye-mediated reading, and reading speed is directly related to the number of fixations and the average fixation duration. The region of effective vision during reading is referred as perceptual span, and it is also directly involved in gathering information necessary to program the next saccade. The number of letters per forward saccade (L/FS) represents an indirect measure of perceptual span. Patients with central scotoma use their PRL to read text instead of fovea, and reading speed is severely affected in these cases. In AMD eyes, L/FS index and thus perceptual span is drammatically compromised, this effect is mediated by number of fixations. More recently, nonuniformity of eye fixations (NUF) factor has been considered a new predictor of reading speed, it basically reflects increasing horizontal coordinates of eye fixations due to words difficult to identify.(12–16)

Although it is no longer commercially available, Rodenstock SLO (Rodenstock GmBH, Munich, Germany) has been used in several studies to quantify fixation stability.(17–20) Fixation stability determined with SLO appears to be poorer, and the estimation of bivariate normal distribution ellipse area represents a well-established way to describe normal fixation. This is based on the assumption that measurements of horizontal and vertical position of the eye have a bivariate normal distribution.(21, 22) Nowadays, the bivariate contour ellipse area (BCEA) is widely accepted as indicator of fixation stability in normal and pathologic eyes, with larger areas corresponding to poorer fixation stability.(22)

The wide fixation variability detected with SLO has several explanations, basically consisting in poor image resolution, the use of a gross scale to measure fixation position, and doubtful vessel landmarks.(22) The limitations of SLO were overcome by the introduction of microperimeter. It allows the evaluation of retinal sensitivity and fixation stability, combining computerized perimetry, measurement of fixation stability and digital fundus photography into one instrument.(23) Not less important, this instrumentation permits to perform visual rehabilitation in pathologic eyes with poor fixation stability.(10)

With the introduction of biofeedback techniques in several fields, a similar approach has been proposed for visual rehabilitation.(10, 24–26) The biofeedback approach increases fixation stability instructing patients to move their eyes according to an audio feedback into a desired final fixation position. Nevertheless, there is no consensus on rehabilitative strategies, sometimes skepticism on the efficacy of the training and inconsistent standard of practice.(2) Behind these issues, an intricate network of information on fixation stability and adaptive strategies in response to a new developed central scotoma. This review will try to serve as a starting point to better understand potentiality, limits and future implications of microperimetric biofeedback training (MBFT). The main topics covered include rationale of the biofeedback training, rehabilitative strategies used and their implications, therapeutic benefits in different ocular diseases and future perspectives.

3. RATIONALE OF BIOFEEDBACK TRAINING

Patients with age-related macular degeneration (AMD) and an absolute central scotoma can improve their visual reading speed using optical aids and peripheral retina above and below the lesion. They use a new, non-foveal retinal area of intact vision to perform visual tasks.(17, 27)

Patients with macular diseases use self-adaptive strategies to use peripheral retina in place of damage fovea. This discrete area of eccentric retina used for fixation is called preferred retinal locus (PRL). The PRL were defined as an area that contains the center of a target image for over 20% of a fixation interval. The PRL, single when it is kept central vision, can become multiple if the scotomatous area increases. In fact, with scotoma diameter greater than 20° multiple PRL can be observed in 60% of cases. Centripetal eye movements (drift or saccades) or a tendency to central fixation would result in high variations of visual acuity and fixation stability.(28, 29)

A preferred fixation area acts as new oculomotor reference, rereferencing eye movements to the preferred fixation area, indicating a sort of oculomotor “adaption”. This phenomenon is present in the majority of patients with long-standing macular diseases. In such cases a better-defined PRL and a re-referenced oculomotor system are more likely to be identified than a newly developed macular diseases eyes.(28–30) Cortical neurons located in retinotopic position corresponding to the scotoma do not receive direct stimulation from this region, having less activation than other cortical neurons. However, those neurons start receiving small activity originating from non-altered neurons nearby, these connections gradually reinforced and the system evolves finally to a new stable state. This model explains neuronal

changes responsible for the adaptive response to a scotoma, and it is essentially considered neuronal plasticity.(31, 32)

Cerebral plasticity seems to be directly involved in both the reorganization of the primary visual cortex after central vision loss as well as after biofeedback training. In fact, a strong activation of visual cortex was noted in patients with central visual loss during fixation using eccentric PRL. It is surprising considering that this cortical activation does not happen in healthy subjects, suggesting a cortical reorganization in eyes with central scotoma. Training induced functional reorganization in visual areas with strongest responsiveness in the blind hemifield in V5 and V3a and the superior temporal polysensory area.(33–35) Although the reorganization of retinotopic cortex has been demonstrated in eyes with central scotoma, conversely eyes with extensive bilateral macular lesion but foveal sparing within 2 degree did not. This finding has been confirmed through monitoring a subject with initial foveal sparing until its involvement. Not surprisingly, the subject exhibited reorganization of visual processing after foveal involvement, confirming that such reorganization is dependent on complete foveal damage.(36, 37) In addition, the oculomotor training increases gray and white matter density in the left semi-lunar lobule of the cerebellum, indicating a learning-effect to perform visual tasks with eccentric viewing.(38)

The microperimetric biofeedback reinforces PRL improving visual cortex activation. The audio feedback may further increase attention modulation helping the brain to detect the final PRL. Moreover, the acoustic biofeedback probably facilitates communication between intraretinal neurons as well as retina-brain transmission supporting a “remapping phenomenon”.(10, 39) Not less importantly, microperimetric biofeedback improves quality of life as reported by visual function questionnaire.(40) In specific, patients report to be more autonomous than before training, with improvement of near activities and mental health as well as reduced need for help.(38, 41)

The proper identification and knowledge of PRLs’ behavior is essential to any low-vision rehabilitation attempt. Two main features are considered in the PRL evaluation, fixation stability and location. Fixation stability represents horizontal and vertical variances during fixation of a steady target image. In fact, while one eye fixates on a stimulus minimal fixational eye movements along vertical and horizontal meridians are detected and an ellipse whose area is analogous to the standard deviation of a univariate distribution can represent their dispersion.(21, 30, 42) Fixation stability is affected in eyes with central vision loss, contributing to their poor visual performance.(23, 43) Location of fixation area corresponds to the PRLs position into visual field. The PRLs is not conscious, and the mechanisms involved are widely unknown. However, the PRLs occur more frequently in the inferior or the left part of the visual field, and typically at the border of the scotoma.(44, 45)

3.1. Preferred retinal loci (PRLs)

The PRL develops simply through experience a central scotoma, without any formal training. The newly formed PRLs can be multiple, but the spontaneous localization of PRLs does not always correspond to the ideal one for a given task.

Otherwise, eccentric-viewing training could facilitate this behavior, making fixation more stable and accurate. The majority of the PRLs occurred in the upper and the right quadrant of the retina, which correspond to the inferior and left parts of the visual field.(23, 45, 46) It has been reported that the preference of lower visual field is important for ocular locomotion, ensuring a better reading performance than other visual field locations.(47) However, sometimes patients can use multiple and distinct PRLs, the superior is used for the global viewing and the left and right PRL are employed to improve letter discriminations or vice versa. Accordingly, PRL function does not depend solely by the position in relation to the scotoma.(44, 48)

Lei and Schuchard reported that some patients can use two different PRLs under different lighting conditions. These PRLs develop spontaneously in the visual system’s effort to self-adapt during daily activities. The visual system appears to prefer the PRL with high stimulus illuminance (PRLhi) that are usually located within the relative scotoma or just outside the dense central scotoma. Conversely, PRL with low stimulus luminance (PRLlo) is used in poor lighting condition, and it is usually located within an area of relatively healthy retina.(49)

Riss - Jayle *et al* also showed that the success of a rehabilitation strategy is independent from eccentricity of the PRL, and thus all subjects affected by a central scotoma can be treated in order to improve their residual vision. However, there is one exception to this rule: when a PRL is placed 20 degrees far away from the center it loses its effectiveness because it no longer meets the necessary oculomotor criteria. The most important condition for the success of a rehabilitation program is the presence of a PRL, otherwise it is mandatory to wait till it will be established. The PRL “chosen” by the patient, however, is not always the best to ensure an optimal visual performance in a rehabilitation program; in several cases other retinal areas nearby retinal lesion should be considered as potential and better PRL.(50)

The patient usually tends to pick one or more PRLs spontaneously after a certain period of

adaptation and latency of the visual system, and it is usually placed in an eccentric position respect to the scotoma itself. (22) Different PRLs may be elicited during complex tasks such as reading (3), and it could represent an obstacle to successful biofeedback rehabilitation. Several studies investigated this issue with controversial results; Riss Jayle *et al* showed that this phenomenon may be deleterious and it should be bypassed re-educating the eye to a single PRL or selectively training the eye who shows one PRL.(44) Duret *et al* demonstrated that each PRL has a specific task: one is needed to decrypt the beginning of a word, one the end of the word and one its entirety. The patient may have an advantage once aware by proper use of it improving reading performance.(42)

Left-field PRL has been considered disadvantageous because it occludes the upcoming test during English reading, thus the selection of a new and more favorably located fixation training target (FFT)(51) trained retinal locus (TRL) allows to improve reading speed. The eyes with central vision loss show greater advantage from reading with a PRL below the scotoma. Accordingly, the FFTs are usually selected in an area above the retina lesion (below the visual field scotoma) or alternatively in an area below the retina lesion (above the visual field scotoma). This technique was useful either in eyes with unilateral disease in absence of newly formed PRL or in eyes with bilateral disease and PRL located in an unfavorable position for reading.(52, 53).

The FFT develops quickly and easily in almost all the patients trained, and it is associated with a marked increase in reading speed from 9 words/min to 68 words/min.(52, 54)

Reading visual span and character discrimination further influence the reading ability. The reading visual span is defined as the number of characters that can be recognized on a single fixation. The reduction in the size of the visual span is directly related with reduction in reading speed.(55, 56) Global viewing refers to the perception of the word in its entirety, and character discrimination concerns the ability to read individual letters correctly. Although multiple PRLs with complementary function can represent a functional advantage in developing more elaborated reading strategies, spontaneous PRLs not always satisfy all those requirements.(44, 48)

All the above-mentioned considerations should be evaluated before approaching microperimetric biofeedback. The optimal PRL is able to keep the visual image in a discrete and stable retina area (fixation stability), to follow a moving target (pursuit) and rapidly shift the fixation on a desired object away from the PRL (saccadic movements).(11) Patients are often aware of how and when they use multiple PRLs and their locations.(11, 28) Accordingly, the biofeedback training is based on two main approaches, the reinforcement of a self-established PRL if it is located in an advantageous position or the selection of the newly FFT in an area that is more favorable for reading.(52, 57) Beside these main strategies, other hybrid approaches have been reported such as the training of an additional FFT other than self-established PRL.(58)

Déruaz *et al* designed a new rehabilitative procedure based on the use of an additional area, an examiner's selected FFTs other than self-selected PRLs. This FFT was usually selected either above or below the lesion on the SLO image. Subjects were instructed to fixate words by alternating between the initial PRL and the examiner's selected FFT. The training improved reading speed, visual acuity and the gains persisted at three-month follow-up. Noticeably, this training was performed using SLO system, and it did not provide any audio feedback. The patients were verbally assisted to find and learning to use the FFT. (58)

More recently, further studies conducted using microperimetry confirmed that the choice of a more favorable PRL represents a good rehabilitative strategy. The functional outcomes improve drastically after microperimetric biofeedback in patients who suffering from macular and inherited retinal diseases. These improvements regard visual acuity, retinal sensitivity, fixation stability, as well as reading speed. (10, 41, 57, 59, 60)

Tarita-Nistor *et al* conducted a study on PRL relocation using microperimeter MP-1. The new PRL location was chosen in the upper part of the retina in all cases, approximately located at the same radial distance from the old PRL. At the end of training, all the patients developed a new PRL in the upper retina and the BCEA of the new PRL was significantly improved by 53%. The improvements in fixation stability and PRL relocation were accompanied by improvements in reading performance, suggesting that these adaptive changes can result by the plasticity in the visual system or cortical reorganization after bilateral vision loss.(61)

The PRLs have been studied using different type of eye trackers and the SLO.(18–20, 52) Nowadays, the most common device used is microperimeter, it permits to identify PRLs with perfect anatomical correspondence thanks to the superimposition with color fundus photograph. Once the PRL is identified the relocation is driven by the rules previously reported, i.e. above or below the scotoma. In addition, retinal threshold sensitivity map helps to select an area with an appropriate retinal sensitivity to ensure the reinforcement of fixation behavior and fluent reading.(52, 57, 60)

3.2. Fixation stability

Microperimeter quantified fixation stability in two ways: by the proportion of fixation points within 2° and 4° diameter circles centered in the gravitational center of all fixation points, as proposed by Fujii *et al(62)*, and by the BCEA using the formula previously described by Timberlake.(22) The Fujii's classification is no longer used because it does not adequately reflect the elliptical nature of fixation area or the multimodal fixation patterns frequently exhibited by subjects with macular disease. The BCEA has several advantages: it contains more information than the 3-step grading scale, its variability is independent of the magnitude, and its quantitative expression is useful for statistical analysis.(63, 64)

Quantification of fixation stability is usually performed by plotting the position of each fixation on Cartesian axes and calculating the area of an ellipse that encompasses a given percentage of fixation points. The stability of fixation is quantified by calculating a BCEA encompassing 68% of fixation points (±1 standard deviation). This measure is based on the values of the standard deviations of the horizontal and vertical eye movements during fixation and the correlation coefficient (Pearson product-moment correlation coefficient) of the horizontal and vertical eye positions. The BCEA formula (expressed in deg2) is calculated as follows:

$$BCEA = \pi\chi^2\sigma_x\sigma_y\sqrt{1-p^2}$$

where χ^2 is the chi-squared value (2df) corresponding to a probability of 0.6.8.2. (±1 SD), σ_x and σ_y are the standard deviations of the horizontal and vertical eye movements (x and y), and ρ is the Pearson product moment correlation coefficient.(21, 22)

The BCEA can be obtained as an isolated fixation task before microperimetry (static fixation) or recorded during microperimetric examination (dynamic fixation).(65) The increasing PRL distance from the fovea influences the BCEA, determining its enlargement. Moreover, also time since diagnosis and visual acuity positively correlate with the BCEA, indicating that as disease progresses the PRL tends to enlarge and shift farther from the fovea. (17, 18) It has been reported that fixation stability improves with binocular view, the better eye seems to drive the worst one improving fixation stability of 84–100%.(66)

Morales *et al.* analyzed PRL shift during static and dynamic fixation stability recording. They demonstrated that initial PRL (recorded during pure fixation task) and final PRL (recorded during microperimetry) are close each other and located over the fovea centralis in eyes with stable fixation. Conversely, eyes with initial and final PRLs far from each other are mostly characterized by eccentric and with unstable fixation. Moreover in such cases visual acuity is significantly reduced, confirming the relationship between fixation stability and PRL location that are both useful therapeutic target in microperimetric biofeedback.(67)

The PRL training is essentially achieved by the customization of an optimal eccentric viewing via selecting an appropriate FFT, and maximize residual vision by increasing fixation stability. The BCEA improvement is expressed by reduction of elliptical fixation area, and it is considered one of the primary goals after training. Therefore, the evaluation of fixation stability before training is needed to any rehabilitative attempt.(10, 38, 39, 68)

4. BIOFEEDBACK TRAINING APPROACHES

The basic rehabilitative protocol consists of: best-corrected visual acuity assessment, close up visus near visual acuity determined at 30 cm with appropriate refractive correction, reading speed, microperimetry. Such examinations should be obtained before biofeedback training, and then FFT selection can be established under microperimetric guidance. The training sessions are scheduled once a week, and at the end all the above-mentioned examinations are repeated. The duration of each training session is 10 minutes per eye, and usually 10 or 12 sessions are performed. The biofeedback mode is manually selected on the screen. Before training the patient received detailed instruction, and only one eye per session is trained, occluding the fellow one. The patients are instructed to move their eyes according to an audio feedback emitted by the microperimeter. The audio feedback advises them if getting closer or not to the desired final fixation position.(10, 39, 41, 57, 59, 69)

Microperimetry can record fixation stability using an auto eye-tracking system. This system continuously register eye positions relative to anatomical landmark and compensates for stimulus projection location. The anatomical landmarks are manually selected by operator along vascular arcades. An infrared camera captures funduscopic black and white image that is used as reference during MBFT, and a color fundus photograph collected at the beginning can be subsequently superimposed onto microperimetry at the end of the examination. The operator can decide examination protocol and the size and shape of the target. During the examination, patients are advised to fix the target previously selected, and push the handheld button every time a light stimulus is seen. The examination is usually performed in a darkened room. Some authors also used to dilatate the pupils with 1 drop each of tropicamide 1% and phenylephrine 2.5.%.(23)

The most widespread microperimeter is MP-1 (Nidek Technlogies, Padova, Italy). The instrument has a 45° field of view and a display monitor, The background is set at 1.2.7. cd/m2, with a stimulus attenuation ranging from 0 to 20 dB with Goldmann-type size. Stimulus presentation is 200 ms, if the stimulus is not seen within this time frame it is considered as 'not view' and the next stimulus is projected. The strategy of stimulus threshold presentation is usually 4–1 or 4–2-1.(10, 59, 69, 70) The operator customizes the program on the basis of residual visual acuity, scotoma size and disease's type.

The Macular Integrity Assessment system (MAIA; CenterVue S.p.A., Padova, Italy), is a novel MP device that was introduced into clinical practice several years ago. This system reports fixation stability as a percentage of fixation points (PFP) falling inside a circle of 1° or 2° radii in the barycenter of a cloud of fixation points as suggested by Fujii(55) or using BCEA methods as previously reported. (22) The MAIA microperimeter is based on a SLO technology to image the retina using a 36° field of view. The automated retinal eye-tracking system corrects eye movements at 25 Hz with respect to the positioning of the target. The stimulus attenuation ranges from 0 to 36 dB, with a maximum luminance of 1000 asb. The operator can manually select the fixation target size and shape.(51)

The reading speed (words/min) can be measured using black letters on white background at 25 cm or nearer with appropriate refractive correction, using Times New Roman character 1/72 (0.0.1.3.8) inches or 0.3.5.2.77 mm in size. The patient is invited to read all the sentences as fast as possible, without skipping words. The sentences contain upper case letter but not punctuation, and they are composed of non-technical words.(39) Crossland *et al* compared three different reading test and their correlation with BCEA using microperimeter MP-1. The MNREAD chart was used to measure peak reading speed and critical size at 25 cm. Second, rapid serial visual presentation (RSVP) using a system programmed in Matlab that project four sentences, one a time, on a cathode monitor with mean luminance of 50 cd/m. The third was the European reading test, which contains 10 passages of 820–830 characters randomly selected on a printed card at fixed text sized of N20. They reported that RSVP and MNREAD had a direct correlation with the BCEA, and patients read more quickly MNREAD than other tests. The highest correlation was found between peak reading speed and the BCEA. (63)

A 25-item questionnaire (NEI-VFQ-25) can be administered at baseline and after the end of microperimetric biofeedback, completing the patient evaluation. It measures the level of visual disability impact on real life, social functioning, and daily tasks depending on visual function. The test is composed by 12 subscales: General Health (1 question), General Vision (1 question), Near Vision (3 questions), Distance Vision (3 questions), Driving (2 questions), Peripheral Vision (1 question), Color Vision (1 question), Ocular Pain (2 questions), Role Limitations (2 questions), Dependency (3 questions), Social Function (2 questions), and Mental Health (4 questions). The results are expressed on a 100-point scale in which 0 represents the worst and 100 the best score achievable.(40)

All the examinations performed at baseline and last follow-up are almost standard for all the biofeedback strategies used. The MBFT strategies can be summarized into two main group: acoustic biofeedback and structured stimulus biofeedback.

4.1. Acoustic biofeedback

The audio biofeedback consists in a sound emitted by microperimeter that train patients to keep their gaze on a specific position. The operator following the PRLs' rules previously reported(41, 45) decides the specific gaze position, which is marked on black and white retinal image by the operator and displayed as a target to the patient. The tone becomes more continuous as the patient's gaze is close to the selected position, conversely whether eye drifts away from the target the tone becomes discontinuous. The frequency of the auditory signal increases with the fixation toward PRL, and the patients are invited maintain the fixation on PRL as long as possible.(39, 71)

In case of bilateral disease, microperimetric biofeedback is administered to the best or dominant eye.(10, 61, 71) Nevertheless, it has been reported bilateral rehabilitation with similar anatomic-functional characteristics. First, the training was performed in the eye with better fixation stability for 3 weeks and then in both eyes starting every session with the best eye. At the end of visual rehabilitation, all functional parameters significantly improve in both eyes suggesting a beneficial effect of bilateral acoustic Biofeedback Training (BFT) in eyes with small scotoma.(68)

4.2. Structured light stimulus biofeedback

Flickering visual stimulus has been demonstrated to induce cortical reorganization in adult patients after intensive training.(33) This method was applied to microperimetric examination, superimposing a black and white checkboard pattern onto fixation target. The pattern size is selected according to the patient's visual acuity. Patients are invited to fixate target and the stimulus flickered when they keep the fixation within the desired PRL. The reversal checkboard has three different dimension 15'-30'-60' flickering at 4 Hz.(57)

The biofeedback rehabilitation with flickering pattern stimulus is similar to acoustic biofeedback. In fact, it provides a sound that become progressively continuous whenever the fixation is keep on PRL and at that point flickering structured pattern is projected on PRL. Acoustic and flickering pattern BFT are both useful methods to improve functional parameters in rehabilitated eyes but flickering pattern seems to produce more benefit than acoustic BFT. Indeed structured stimuli together with sound could increase reactivation process of the PRL.(71)

5. APPLIED BIOFEEDBACK STRATEGIES

5.1. Age-related macular degeneration

Several factors should be considered in eyes affected by AMD prior to microperimetric biofeedback approach. In brief, central scotoma development induces an adaptive mechanism to improve visual performance by means new retinal locus becoming a “pseudofovea” called PRL. The establishment of eccentric vision further affect the amplitude of microsaccades, thus influencing fixation stability that can increase from 10 to 20 deg^2 in AMD eyes. The scotoma area can also directly affect fixation stability, especially when it exceeds 20 deg. In this case, the fixation improvement after biofeedback training can be limited. The fixation instability in turn reduces reading speed, and even more sophisticated tasks such as face recognition. In fact, AMD patients show fixation patterns similar to patients affected by pathologies involving facial recognition (such as social phobias, Williams syndrome, autism, schizophrenia, or prosopagnosia).(43, 72–75)

Beyond the improvement of fixation stability, the assessment of PRL or multiple PRLs is essential to establish visual rehabilitative strategy. Typically, patients with AMD use a PRL situated on the edge of the scotomatous area,(76) but also multiple task-dependent PRLs e.g. reading or face recognition (77), or brightness.(49) General rules applied in clinical practice has been extensively discussed above. In summary, whether PRL is well-formed and located in an advantageous position it can be reinforced by visual training. Conversely, if the PRL is not formed or located in an unfavorable position, a new retinal locus can be trained (TRL) selecting an area above the retina lesion (below the visual field scotoma) or alternatively in an area below the retina lesion (above the visual field scotoma).(1, 50, 52, 53)

Many studies in literature investigated the potential benefits of rehabilitation treatment in patients with AMD. Herein we report the main rehabilitative strategies used and outcomes reached (see also Table 1). The acoustic biofeedback has been performed in AMD eyes, training one eye once a week per 5–10 consecutive weeks. The duration of each session is usually 10 minutes, but also prolonged session till 1 hour has been reported. At the end of MBFT, all patients showed significant improvement in BCVA, fixation stability, reading speed and retinal sensitivity. Moreover, patients reported a subjective improvement in their daily activities after training, even if no significant benefit was demonstrated on depression. The authors hypothesized that acoustic biofeedback can aid central nervous system to set newly developed TRL by modulating attention and thus educating the patient to use the most beneficial PRL to improve residual vision.(10, 39, 61, 78, 79)

Later, several studies investigated acoustic biofeedback alone or combined with a light stimulus in order to understand the most suitable strategy able to improve both fixation stability and PRL localization. In a case-control study, patients randomly assigned to acoustic biofeedback or luminous flickering (black and white checkboard) were trained with one weekly session lasting 10 minutes for a total of 12 sessions. The results demonstrated an improvement in visual performance in both groups, but luminous flickering group reached better outcomes in fixation stability, reading speed and visual acuity than other.(50) The superiority of acoustic biofeedback associated with structured light stimulus was further corroborated by Amore *et al.* They reported an improvement in fixation stability and reading speed in both groups. However, only patients who received acoustic biofeedback with structured light stimulus demonstrated an improvement in retinal sensitivity.(71)

Another study tested the efficacy of foveal flickering without acoustic stimulation using improved integrated biofeedback system (IBIS). The intensity of the foveal stimulus was chosen based on visual acuity. The patients were treated with 2 sessions per week for a total of 15 sessions, each consisting of 3 applications each for 3 minutes with a short break. Almost all patients improved their BCVA and reading speed (words per minute). Patients were further randomized to receive the training in one eye and placebo in the fellow. The group who received therapy demonstrated an improvement in BCVA, reading speed, color and contrast sensitivity, as well as visual field. This study further confirmed the efficacy of visual structured stimulus in biofeedback training, suggesting that on-off receptors activation could send a high quantity of macular stimuli to the visual cortex.(25)

5.2. Nystagmus

Auditory biofeedback leads to reduction of both nystagmus amplitude and frequency, with an improvement in visual acuity and contrast sensitivity. (80–82) Mezawa *et al*(83) reported a significant decrease in nystagmus intensity and foveation time,

Table 1. Summary of microperimetric biofeedback training studies

Study	Disease	Study Description	Intervention	Duration	Outcomes[1]
Amore *et al* (71)	AMD[2]	30 patients randomized into 2 groups receiving different intervention	AB[3] vs AB plus LB[4]	10-minute/ twice a week for 5 weeks	AB group: BCEA[5] and reading speed; LB group: BCVA[6], near VA[7], BCEA, RS[8] and reading speed; CS[9] =
Vingolo *et al* (57)	AMD	30 patients randomized into 2 groups receiving different intervention	AB / AB plus LB	10-minute/weekly for 12 sessions	BCVA, reading speed, RS, FS[10] in both groups; LB>AB in FS and reading speed;
Vingolo *et al* (39)	AMD	27 eyes (15 patients)	AB solo	10-minute/weekly for 10 sessions	BCVA, near VA, FS, reading speed and RS
Tarita-Nistor *et al* (61)	AMD	6 eyes (6 patients)	AB	1-hour/weekly for 5 sessions	BCEA, PRL relocation, reading speed.
Pacella *et al* (78)	MIX	122 eyes AMD 49 eyes myopic maculopathy	AB	9-minute/weekly for 16 sessions/ 1-year follow-up	BCVA, RS, FS, and reading speed in both groups; significant FS worsening at 12 months;
Vingolo *et al* (10)	MIX	1 eye post-traumatic macular scar, 2 eyes vitelliform distrophy,2 eyes Cone dystrophy,2 eyes Stargardt disease	AB	10-minute/weekly for 10 sessions	BCVA, near VA, reading speed, FS, RS and 22-item questionnaire on quality of life;
Grenga *et al* (69)	Nystagmus	Case report with oculocutaneous albinism	AB	10-minute/weekly for 10 sessions	BCEA, no significant changes in BCVA and RS;
Vingolo *et al* (59)	Myopic maculopathy	17 patients (34 eyes)	AB and Visual Pathfinder	7-minute/weekly for 10 session (AB) 3-minute/ weekly visual pathfinder	BCVA, pev p100 amplitude, RS, reading speed, BCEA and FS;
Rajiv Raman *et al* (85)	Myopic maculopathy	Case report, bilateral (2 eyes)	AB	10-minute/weekly for 10 sessions, on alternate days for both eyes;	BCVA, fixation location and stability till 1-year follow-up;
Verdina *et al* (86)	Stargardt	18 eyes (18 patients) subdivide into two groups: 12 eyes treated and 6 eyes as controls	AB	10-minute/weekly for 8 sessions in the better eye	Treatment group: FS, reading speed and RS.Control group: same or worse.
Scuderi *et al* (41)	Stargardt	Case report, bilateral (2 eyes)	AB	10-minute/weekly for 10 sessions repeated at 3,6,12 months;	RS, reading speed, FS and NEIVFQ score 25 item till 12-month.
Verboschi *et al* (70)	POAG[11]	18 eyes (10 patients)	AB	10-minute/weekly for 10 sessions repeated at 4,8,12 months	FS, BCVA, reading speed, NEI-VFQ 25 items test and RS.
Ueda-Consolvo *et al* (60)	Post-surgical MH[12]	9 eyes (9 patients)	AB	10-minute/session repeated at least 3 times within 3 month	BCVA, reading speed and FS;
Vingolo *et al* (89)	Post-retinal detachment surgery	52 eyes randomized into 2 groups:group A: 25 eyes (12 SB[13] and 13 PPV[14]) treated B: 27 eyes (13 SB and 14 with PPV) controls;	AB	10-minute/weekly for 10 sessions	Group A: BCVA, FS and RS;
Salvatore *et al* (90)	Glaucoma / macular pucker	Case report, bilateral (2 eyes)	AB with Sonata for two pianos in Dmajor K 448	10 –minute/weekly for 5 sessions	FS and NEI-VFQ 25 item questionnaire in both eyes, BCVA in one eye and remained stable in the fellow, RS in one eye and worse in the fellow;

Ouctomes[1]: functional outcomes significantly improved at the end of follow-up; [2]AMD: age-related macular degeneration; [3]AB: Acoustic biofeedback; [4]LB: luminous flickering structured pattern; [5]BCEA: bivariate contour ellipse area; [6]BCVA: best-corrected visual acuity; [7]VA: visual acuity; [8]RS: retinal sensitivity; [9]CS: contrast sensitivity; [10]FS: fixation stability, expressed as fixation points within 2 and 4-degree; [11]POAG: primary open-angle glaucoma; [12]MH: macular hole; [13]SB:scleral buckle; [14]PPV: pars plana vitrectomy.

which is basically time spent by the eye into stable position in a certain point of the retina. It has been hypothesized that changes in muscular tone of the laryngeal or pharyngeal muscles may modulate the intensity of nystagmus, because of their common embryological origin.(82, 83)

To date, microperimetric auditory biofeedback has been described in a case of bilateral albinism-related nystagmus. The low-vision rehabilitation consisted of 10 training sessions of 10 minutes for each eye, performed once a week using the MP-1 biofeedback examination. The BCEA significantly improved after training but BCVA and mean retinal sensitivity did not change compared to baseline. The improvement of the BCEA was accompanied by reduction of horizontal eye movements, hypothesizing that biofeedback therapy is an effective tool to reduce ocular nystagmus.(69)

5.3. Myopia

A small number of studies investigated the implications of biofeedback treatment in pathologic and non pathologic myopia. The efficacy of auditory biofeedback on myopia was first demonstrated using Visual Training system in mildly myopic (< or = -3.5. D) eyes. In this study, the acoustic tone frequency was driven by patient's ability to modify their accommodative status, and thus high pitched tone correspond to relaxed accommodative status. They were divided into two groups one who received auditory biofeefback and controls. Myopia worsened in both groups (treated and control myopes), whereas visual acuity collected using standard chart was significantly improved but it was unchanged when measured by computer. However, an improvement in psychometric scores was detected, confirming that biofeedback visual training had a positive effect on psychological distress correlated with myopia and on subjective VA.(84)

The relationship between myopia and biofeedback training has been studied also in myopic maculopathy. The acoustic biofeedback has been considered useful in such cases, especially in ameliorating fixation stability and reading speed.(10, 78) More recently, a study investigated the efficacy of the MP-1 microperimeter and Visual Pathfinder (LACE Inc) in improving visual function in eyes with central scotoma due to myopic maculopathy. The patients underwent 10 training sessions with MP1 biofeedback (7 minutes) and Visual Pathfinder (3 minutes) for each eye once a week. After the treatment, patients showed an improvement in BCVA, PEV p100 amplitude, average retinal sensitivity, fixation stability. The authors concluded that the combination of those treatments could be effective in myopic maculopathy, suggesting a possible adjuvant "therapeutic option" in such cases.(59)

The usefulness of MBFT was also investigated in a case of bilateral myopic macular degeneration, reporting functional outcomes after one year of follow-up. The eyes were not trained within the same session, but they received 10-minute training on alternate days. The improvement in BCVA, fixation location and stability was maintained at 1-year follow-up, suggesting also a long-standing efficacy of microperimetric biofeedback.(85)

5.4. Stargardt disease

A pilot study previously described successful functional outcomes in a patient with Stargardt disease who received bilateral acoustic biofeedback training. (10) Such results were further corroborated in a larger case control study including 18 eyes. Patients with unstable fixation and BCVA between 20/100 and 20/320 in the best eye were recruited. They were subsequently divided into two groups, one who received biofeedback rehabilitation and the other group served as controls. The rehabilitation protocol consisted in 10-minute session, once a week for 8 consecutive weeks, in the eye with the best BCVA. The FFT was chosen in a 2° circle area with best retinal sensitivity located superiorly respect to the fovea. The MBFT group showed an improvement in fixation stability, retinal sensitivity, and reading, specifically related with the training. Otherwise, BCVA and contrast sensitivity demonstrated only modest changes and not statistically significant.(86)

Later, another case report reported bilateral acoustic biofeedback training in a Stargardt patient. The TRL was chosen in a 3-degree area superior to the anatomical fovea with good retinal sensitivity. The rehabilitation protocol consisted of 10 sessions once a week in both eyes, training was repeated at 3, 6 months and 1 year. In this case, beside functional outcomes also NEI-VFQ 25-item questionnaire score demonstrated a significant gain after training.(41)

5.5. Other Conditions

The benefits of biofeedback rehabilitation techniques have also been investigated in other diseases, such as advanced glaucoma, retinal detachment and macular hole after vitreoretinal surgery. In such cases, training selection criteria mostly included fixation instability, and thus not necessarily a PRL displacement from anatomical fovea. In fact, glaucoma is usually characterized by a preservation of central visual function until late stages of the disease, but an unstable fixation has been described already in early and moderate stages of primary open-angle glaucoma (POAG).(87) The fixation stability in advanced POAG seems to be directly related to retinal sensitivity within 10-degree.(88)

Nevertheless, to date, only one report investigated the ability of MBFT to maximize the residual visual function in eyes with advanced POAG. The advanced stage POAG was defined as a cup-to-disk ratio> 0.7. or asymmetry of at least 0.2., BCVA <20/200, advanced visual field damage including mean defect <24dB and an island of residual vision in central or temporal location, and evidence of glaucoma damage in the contralateral eye. The rehabilitation program consisted in 10 sessions of 10 minutes once a week using acoustic biofeedback technique. The training was repeated at 4, 8 months and 1 year. At the end of the program 13 of the 18 eyes showed an increase in fixation stability, passing from relatively unstable to stable and location changed from predominantly eccentric to predominantly central. Moreover, BCVA, reading speed, NEI-VFQ score to 25 items and retinal sensitivity showed a statistically significant increase after training.(70)

Post-surgical biofeedback training was used in primary retinal detachment treated with scleral buckle or pars plana vitrectomy. The patients were randomly assigned to rehabilitation group or standard postoperative care with no further rehabilitative therapy. The rehabilitation protocol started 15 days after stopping cycloplegic eye drops or after silicone oil removal in patients who underwent pars plana vitrectomy. The patients were subjected to acoustic biofeedback training, and re-educated to fix with a new PRL chosen upon microperimetric evaluation by the operator. The post-training outcomes were evaluated till 18 weeks of follow-up, demonstrating a significant improvement in BCVA, fixation stability and retinal sensitivity. It has been suggested that microperimetric rehabilitation could speed up visual recovery time after surgery.(89) Consolvo *et al*(60) applied the same biofeedback strategy in eyes with poor functional recovery after macular hole surgical repair. Patients with BCVA less than 0.6. after 3 months despite proper anatomical closure of the macular hole were enrolled. The new PRL was chosen within central 2-degree according to the retinal sensitivity. The 10 minute-training was repeated at least three times within three months. After training, patients demonstrated a significant increase in visual acuity, whereas reading speed and fixation stability did not change significantly.(60)

The MBFT was also used in other degenerative retinal diseases such as adult pseudovitelliform dystrophy. Since the disease is characterized by an almost symmetric anatomical and functional status, the acoustic biofeedback was performed in both eyes. The training was set up starting from the eye with better fixation and then both eyes in the same session. All functional parameters, including reading speed, retinal sensitivity and fixation stability, ameliorated at the end of follow-up.(10, 68)

6. NEW PERSPECTIVES

In a case report by Salvatore *et al*(90) was introduced “Sonata for two pianos in D major K 448” as sound in an acoustic biofeedback program. The patient underwent a rehabilitation protocol consisting of 10-minute training for 5 consecutive weeks in both eyes. The patient was instructed to move his eyes according to a monotone sound which became Mozart’s sonata whenever the patient fixed the desired position. The training improved fixation stability in both eyes, but BCVA and retinal sensitivity increased in one eye solely. The score of the NEI-VFQ 25 item questionnaire was increased. Since Mozart’s sonata was previously reported to increase visual-spatial performance, the authors intended to further enhance synaptic plasticity and neural capacity during PRL learning procedure.

Several studies investigated ocular movements abnormalities in depression, schizophrenia, bipolar and obsessive compulsive disorders, suggesting that rapid and saccadic movements provide selective index of cognitive function.(91–94) Nevertheless, only one study assessed fixation features in major depressive disorder and their modifications after therapy using microperimetry. This study showed that retinal sensitivity and fixation stability is significantly reduced in depressed patients, and BCEA area was wider than in healthy controls. Psychiatric patients may potentially benefit from rehabilitative strategies, but this hypothesis deserves further insights.(95)

The application of microperimetric biofeedback should be encouraged in pediatric diseases such as nystagmus and amblyopia. Considering that MBFT could directly modulate cerebral plasticity, this effect may be theoretically more pronounced in young patients.(10, 39) Nevertheless, albinism-related congenital nystagmus demonstrated reduction of the BCEA and horizontal eye movement, no further studies were conducted.(69) In amblyopic eyes a macular scotoma was detected, and preliminary results demonstrated functional improvements after visual training rehabilitation using visual structured stimuli.(96, 97).

7. SUMMARY

Patients with long-standing scotoma usually develop a new self-trained locus of preferential fixation. Microperimetric biofeedback helps to reinforce the self-PRL or to use a newly FFT chosen by the operator in a more advantageous area for reading. The microperimetry allows to obtain a perfect anatomical correspondence of the PRL location, and even to select a locus with good threshold sensitivity. The reinforcement is obtained by increasing fixation stability, reeducating eye to an eccentric viewing. The

therapeutic rationale of MBFT is to improve visual cortex activation facilitating a remapping phenomenon.

The MBFT strategies can be summarized into two main group: acoustic biofeedback alone or combined with structured stimulus biofeedback. The first one uses an acoustic tone that help the patient to maintain gaze on a desired position. The second adds a superimposed checkboard pattern onto fixation target other than acoustic tone, reinforcing cortical reorganization. The results demonstrated greater functional outcomes after acoustic combined with structured visual stimulus. Functional outcomes improvement include visual acuity, retinal sensitivity, fixation stability and reading speed as well. Patients also reported a subjective improvement in the quality of life after training.

Several diseases may benefit of microperimetric training, basically all the disease suffering from central scotoma and unstable fixation. However, promising results have been reported in other diseases not necessarily involving central vision. For instance, patients affected by nystagmus could reach a reduction of horizontal ocular movements. Other diseases included post-surgical biofeedback training in eyes with macular hole or retinal detachment, whose need to be reeducated in use their own fovea or eventually a new developed pseudofovea. The MBFT seems to be promising in post-surgical rehabilitation, to reeducate eyes who temporary lost the ability to use their physiologic fovea. Moreover, considering the greater cerebral plasticity of pediatric patients than adults, further studies would be desirable also in this field.

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Abbreviations: MBFT: Microperimetric Biofeedback Training, LVR: Low Vision rehabilitation, SLO: scanning laser

ophthalmoscope BFDT: biofeedback training; PRL: preferred retinal locus; TRL: trained retinal locus; FFT: fixation training target; BCEA: bivariate contour ellipse area; PFP: percentage of fixation points; RSVP: rapid serial visual presentation.

Key Words: Microperimetric biofeedback, Visual rehabilitation, Microperimetry, Fixation stability, Review.

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